EXPERIMENTAL STUDIES IN DIABETES:

SERIES II. THE INTERNAL PANCREATIC FUNCTION IN RELATION TO BODY MASS AND METABOLISM.

IV. PANCREATIC CACHEXIA.

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Notice of the subject of cachexia is necessary in connection with this series of papers, particularly with a view to the possible criticism that undernutrition treatment represents merely a suppression of glycosuria by cachexia, which may mask the diabetic condition without benefiting it. For the sake of unity other aspects of cachexia must be included in the same paper. They add further to the similarity between clinical and experimental diabetes and thus strengthen the application of results gained with the one form to the other. The marked and rapidly fatal cachexia of totally depancreatized dogs, and their deficiency of wound-healing power and liability to infection, have been known from the time of Minkowski. Attention was previously given[1] to Hedon's "diabetes without glycosuria" and to cachectic disorders in partially depancreatized dogs with or without glycosuria. The present observations will be discussed under the following headings:

Acute deaths following operation.
Subacute and chronic pancreatic intoxication.
Diabetic asthenia.
"Gangrene."
Collapse and prostration as related to glycosuria.
Prolonged cachexia.

ACUTE DEATHS FOLLOWING OPERATION.

Deaths from infection occur sometimes, evidently due in part to diabetic lowering of resistance. Clean surgery prevents peritonitis even after total pancreatectomy, until after some days pus may burrow through all the suture lines. Young diabetic animals are as subject to distemper as human patients to tuberculosis.

The highest non-infectious mortality occurs in senile, obese dogs, generally within one to three days after operation, with an extreme and progressive prostration, generally without glycosuria or acidosis. Dogs in advanced senility without obesity ordinarily pass through such operations safely. Likewise young obese dogs generally survive the operation easily, though when the obesity is extreme and there is much trauma of the pancreas remnant death may occur from the so-called "fat necrosis." At corresponding intervals after operation, examination of the animals which survive with those which succumb shows no perceptible difference in the changes either in and about the pancreas remnant or in the fat elsewhere. It can only be supposed that senility lowers the resistance to the toxic action of the pancreatic juice.

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[1] Allen, F. M.: Studies Concerning Glycosuria and Diabetes, 1913, chapter x.

Pregnant animals, regardless of their nutritive state, are known to be highly susceptible to pancreas operations, which are generally followed by abortion and death within one to several days, though various other abdominal operations may be borne safely. As the fatal result is sometimes so early, it is difficult to ascribe it always to septicemia or other secondary consequences of the abortion, and a special susceptibility of the pregnant animal to pancreatic poisoning seems probable.

Prophylaxis of the fatalities in both obese and pregnant dogs has been attempted by two methods, namely, by preliminary intraperitoneal injections of watery extract of dog pancreas and by preparatory removal of small portions of pancreas. The benefit of either method was doubtful. A very old and fat dog sometimes dies from the quick removal of a small fraction of the pancreas. During the period of injections or successive operations the animal sometimes loses considerable weight, and a diminished susceptibility may be thus explainable. A few successful results were obtained with preparation by either method, but a few were also obtained without preparation.

The above statements are based upon a large series of observations, most of which are included in preceding or subsequent papers. For the sake of brevity it has seemed best to omit individual protocols in this place.

SUBACUTE AND CHRONIC PANCREATIC INTOXICATION.

After the usual partial pancreatectomy, which leaves a remnant communicating with its duct, dogs are sometimes more or less depressed and unwell for several days, and lose weight rapidly, partly on account of indigestion and diarrhea. Swelling and inflammation are generally evident in the pancreas remnant during this period. Still greater decline of weight and strength are commonly found when a portion of pancreas is left isolated from its duct, either in the peritoneal cavity or under the skin. The disturbances are generally transitory, continuing a few days or weeks according to circumstances. They are evidently due to toxic products of pancreatic tissue which is inflamed or undergoing absorption. The early wasting and other symptoms are therefore not attributable entirely to the diabetes, and care should be used in the interpretation of any metabolic observations during this period. Later under suitable conditions the animals are able to digest reasonably well, gain weight and behave normally except for their diabetic tendency, and then are reliable test objects for metabolic study.

DIABETIC ASTHENIA.

If a totally depancreatized, a partially depancreatized and a phlorizinized dog lose equal quantities of sugar in a given time, the totally depancreatized animal will ordinarily show weakness and depression out of all proportion to the other two, and will die while the others are still strong. Even if the totally depancreatized animal appears lively a test with running reveals his lack of strength. The asthenia of partially depancreatized dogs generally appears late in the period of advanced emaciation. Exceptional partially depancreatized animals show early asthenia and rapid progress to death, almost equal to the consequences of total pancreatectomy. These results seem to be classifiable under three headings: (*a*) Small size of remnant; (*b*) inflammation in remnant; (*c*) unknown causes.

(*a*) Small size of remnant.

Occasional dogs with very small pancreas remnants are strong and long-lived. An example previously published[2] was dog 19, which had only about one-fifty-fourth of the pancreas, and died in an operation two and a half months later, having been very vigorous for a severely diabetic animal in the meantime. As a rule, animals with very small remnants suffer not only from poor digestion but also from a more rapid decline than can be accounted for by indigestion. Some instances of exceptionally rapid decline are the following:

DOG B2-64.

Male, bulldog mongrel; brindle; age five or six years; medium flesh; weight, 14.7 kilos. May 25, 1914, removal of pancreatic tissue weighing 26.5 gm. Remnant about main duct estimated at 1.35 gm. ($\frac{1}{20}$ to $\frac{1}{21}$). Glycosuria was checked by intermittent fasting and meat feeding, so as to be absent part of the time and never above 1 per cent. (2.6 to 12.8 gm. daily output). Nevertheless, the asthenia was out of proportion to the loss of weight, and exceeded that of other fasting partially depancreatized diabetic dogs. June 15, at a weight of 9.6 kilos, 0.2 gm. of pancreatic tissue was removed for examination. June 20 the dog was sacrificed when moribund. The pancreas remnant weighed 1.1 gm., and the autopsy otherwise was negative. Microscopically, the tissue on June 15 was normal except for marked vacuolation of islands, while that on June 20 showed recent inflammation in addition.

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[2] (Ibid.), pp. 480, 962.

Though life was not extremely short, the noticeable feature was the disproportionate cachexia in comparison with the glycosuria.

Dog D4–75.

Male; bull terrior mongrel; brindle, aged four or five years; slightly thin; weight, 13 kilos. January 19, 1917, removal of pancreatic tissue weighing 35.3 gm. Remnant about main duct estimated at 2 gm. ($\frac{1}{18}$ to $\frac{1}{19}$). The rapidity of decline and the deficiency of healing of the abdominal wound resembled total pancreatectomy. On January 26 the dog was very weak and was killed. The general autopsy was negative grossly and microscopically. The pancreas remnant was swollen and weighed 5.9 gm. Microscopically there was extreme inflammation; the acini stained irregularly and were in various stages of involution and repair; islands were scarce and small and showed early vacuolation.

In this animal the two factors, small size and inflammation of remnant, were evidently combined.

Cats are more subject than dogs to this form of cachexia. They become diabetic with remnants between one-fourth and one-fifth of the pancreas, and when the remnant is much smaller there is cachexia resembling that of total pancreatectomy.

Cat A1–80.

Female; maltese; young adult; slightly thin; weight, 2¾ kilos. November 13, 1913, removal of pancreatic tissue weighing 5.4 gm. Remnant about main duct estimated at 0.4 gm. ($\frac{1}{14}$ to $\frac{1}{15}$). The animal showed characteristic depression, weakness and poor wound healing, without peritoneal infection, and refused all food. The urine record was as follows:

Date.	Volume, c.c.	Glucose, per cent.
November 13	60	0
14	100	2.8
15	90	3.8
16	40	3.3
17	80	6.0
18	80	2.7
19	65	2.8
20	50	2.9
21	35	3.1
22	40	4.0

Death occurred November 22, at a weight of 1800 gm. The urine recorded is that found in the bladder at autopsy. In contrast to the emaciation of trunk and limbs there was a surprising quantity of omental and peritoneal fat. The pancreas remnant was swollen and hard and weighed 1.5 gm. Microscopically it showed much inflammation and fibrosis, together with the usual diabetic vacuolation of islands. The other viscera were normal grossly and microscopically, except for slight fattiness of the liver and the Armanni vacuolation of renal tubules.

CAT A1-81.

Female; young adult; gray striped; good condition; weight, 3 kilos. November 14, 1913, removal of pancreatic tissue weighing 8.3 gm. Remnant about main duct estimated at 0.4 gm. ($\frac{1}{21}$ to $\frac{1}{22}$). The animal ate about 25 gm. meat on November 16 and 17. Otherwise the clinical course was characterized by refusal of food, profound asthenia and rapid decline, with the following urine record:

Date.	Volume, c.c.	Glucose, per cent.
November 14	20	0
15	75	1.5
16	50	3.6
17	50	7.1
18	80	2.5
19	70	1.6
20	60	0.7

The cat was found dying on the morning of November 21 and was killed. The weight was 2 kilos. The liver was very large and fatty, the other viscera normal. The pancreas remnant, normal in appearance and consistency, weighed 0.6 gm. Microscopically it showed fibrosis, chiefly of interlobular type. The acini were in all stages of fulness, emptiness and involution. Islands were almost impossible to find in a series of eight slides containing four sections each. One definite one was found in the last stages of hydropic exhaustion. The others were apparently reduced to small clumps of alpha cells, the identity of which could sometimes be suspected but not clearly demonstrated amid the inflammation. The process of functional exhaustion was thus exceptionally rapid.

(*b*) Inflammation in remnant.

DOG E5-12.

Male; Dalmatian; aged three years; good condition; weight, 16.25 kilos. March 23, 1917, removal of pancreatic tissue weighing 40.5 gm. The attempt was made to leave a remnant small enough to permit diabetes, yet extending the whole length of the uncinate process. The remnant left consisted of the duct and bloodvessels, with a narrow band of accompanying parenchyma. The dog showed slight appetite on the first two days, but was not fed. There was marked and increasing prostration like that following total pancreatectomy, with the following urine record:

Date.	Volume, c.c.	Glucose, per cent.
March 23	370	Slight
24	146	1.7
25	810	2.9
26	470	1.8
27	468	3.8
28	248	3.3
29	328	2.4

The dog was found dying on the morning of March 30. There was intense inflammation of the pancreas remnant and distinct congestion and edema of the hypophysis, otherwise nothing unusual in the autopsy.

Dogs C3-83 and D4-16.

Dog C3-83 became diabetic after removal of five-sixths of the pancreas on April 20, 1916, and dog D4-16 after removal of $\frac{11}{12}$ of the pancreas on the following July 14. The two animals were used for parallel experiments, involving similar glycosuria and other conditions. The contrast in the strength of the two was striking throughout. Dog D4-16 died August 23 while the other dog was still vigorous. The protocols are not given in detail because nothing could prove that some extraneous factor was not the cause of the difference. The number of such observations furnishes evidence that the peculiarity is not accidental. One noteworthy feature in the present instance is the hypertrophy of the pancreas remnant of Dog D4-16, which was estimated at 4.4 gm. at operation and found to weigh 8.2 gm. at autopsy. It thus weighed actually more than the remnant of dog C3-83, which did not hypertrophy. It consisted of normal appearing acinar tissue without fibrosis, with varying numbers of islands. The digestive power should therefore have been as good as in dog C3-83. On the other hand, other studies indicate that the hypertrophy is an indication of preceding inflammation.

(*c*) Unknown causes.

Dog E5-26.

Male; Newfoundland; black, aged three years; good condition; weight, 24.1 kilos. April 25, 1917, removal of pancreatic tissue weighing 33.7 gm. Remnant about main duct estimated at 5.7 gm. ($\frac{1}{7}$). Glycosuria was absent until bread was fed on April 27 and thereafter was heavy. The dog maintained good appetite and cheerfulness, and behaved normally except for surprising weakness, such that he could stand or walk only with great effort. On May 6 the diet was changed to 200 gm. suet, which was fed daily until May 14, after which lung was added. The glycosuria rapidly diminished and was absent after May 11, and strength was regained at a corresponding rate, even on the protein starvation. The animal remained strong thereafter in the aglycosuric condition. Such asthenia in early diabetes and gain of strength on complete fasting are sufficiently familiar in human diabetes, but are rare in dogs. No special cause was found in the later history or autopsy of this animal.

CAT B2-06.

Male; yellow and white; old; very fat; weight, 4.2 kilos. May 12, 1914, removal of pancreatic tissue weighing 8.4 gm. Remnant about main duct estimated at 2.9 gm. (¼). The animal ate well and showed heavy glycosuria on milk and meat feeding. At the same time the weakness was marked and progressive, and death occurred June 1 at a weight of 2.8 kilos. The bladder at autopsy contained 55 c.c. urine, with 1.8 per cent. sugar. Except for the very fatty liver, nothing noteworthy was found in the viscera. The pancreas remnant, normal in appearance and consistency, weighed 1.9 gm. Microscopically there was no inflammation or fibrosis except a trifle at the margins. The acini were normal except for minimal zymogen content, which may explain the small weight of the remnant. Islands were present in fair number but were maximally vacuolated.

Remarks. Asthenia is known as a prominent symptom of diabetes, which occurs in the late stages of diabetes in all patients and animals, along with emaciation and other severe disturbances. It occurs much earlier in some patients, most totally depancreatized dogs and in exceptional partially depancreatized animals. Patients generally regain strength under treatment in proportion to the diet they become able to assimilate, but a few continue to complain of weakness even when free from glycosuria and hyperglycemia on diets which are theoretically adequate. Possible causes of asthenia may be considered as follows:

(*a*) *Loss of Body Fat.* In patients asthenia may be out of proportion to the state of apparent nutrition, may even be present with obesity, and varies between individuals independently of the body weight. Depancreatized dogs, especially if obese before operation, may die while still rich in fat, and at all stages are weaker than normal dogs with a corresponding degree of emaciation.

(*b*) *Loss of Sugar or Nitrogen, or Both.* The above experiments did not include nitrogen analyses, but there is little doubt that phlorizinized dogs, unless they happen to die from acidosis, may far surpass totally depancreatized dogs in strength and in duration of life, while losing even greater quantities of both glucose and nitrogen. Patients sometimes exhibit asthenia when their carbohydrate and nitrogen balance are still fairly favorable, and the great majority of them gain strength under fasting and reduced diet[3] even though they lose sugar and nitrogen during the process.

(*c*) *Severity of Diabetes.* If the severity of diabetes be judged by the D:N ratio and respiratory quotient, it is known that totally depancreatized dogs do not necessarily exhibit the maximal ratio, especially during fasting; also partially depancreatized dogs in the later stages of their diabetes may show maximal ratios (and presumably corresponding respiratory quotients) while retaining greater strength and liveliness and living much longer than totally depancreatized animals. If severity be judged by lack of island tissue, a resemblance exists between animals which have had the pancreas completely removed, or in which the remnant is of minimal size or damaged by inflammation, or in which all the beta cells have been lost by hydropic degeneration, as in some of the examples given above. But many animals retain fair strength and live for a number of weeks or months after their beta cells are thus lost, while many patients and occasional animals (*cf.* dog E5–26 above) exhibit marked asthenia while the diabetes is still early and mild. In human cases the asthenia is not even a sign of intrinsic severity, for it is complained of in many cases which are benign and easily controllable throughout. Cases with asthenia out of proportion to the apparent nutrition after cessation of glycosuria are generally grave, but not more so than many others in which the strength is longer retained.

(*d*) *Nervous Influence.* A neurotic element may be assumed in many patients, whose nervous systems are specially susceptible to the depression of diabetes. Some differences in this respect may be supposed to exist also between animals, but a more important cause is indicated by the fact that in them the asthenia so often progresses to early death.

(*e*) *Indigestion.* Totally depancreatized dogs and those with very small remnants naturally suffer from impaired digestion and diarrhea. Whether the cause be purely an enzymatic or partly an endocrine deficiency, pancreas feeding in numerous trials in this series has never been able to restore anything like normal digestion. But the differences in strength are found also in fasting animals, and the asthenia of human patients seldom has any relation to digestion.

(*f*) *Intoxication.* In some animals absorption of pancreatic poisons may play a part, but this is obviously not the case after total pancreatectomy, and it is seldom to be suspected as a cause of the asthenia of human patients. Acidosis is accompanied by a similar and very profound weakness in both patients and animals, but this factor was excluded in the animal experiments, and the type of asthenia in question is often found in patients without acidosis.

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[3] Ergometric tests in patients were made by J. R. Williams, Arch. Int. Med., 1917, xx, 399–408.

Toxemia of intestinal or unknown origin is assumed by some writers in connection with human diabetes, but there is no reason why totally or partially depancreatized dogs, especially if fasting, should suffer from intestinal intoxication, and the assumption of unknown toxins merely cloaks ignorance and confuses the problem unless some proof of their existence is produced.

(*g*) *Endocrine Deficiency.* Asthenia is a fairly common symptom of endocrine deficiency, even in cases which involve no impairment of nutrition in the ordinary sense. Addison's disease and some hypophyseal disorders are familiar examples. The most probable theory of diabetic asthenia, aside from the part which is explainable by impaired food assimilation, is that it is an effect of the lack of pancreatic hormone either upon the body cells directly or upon other organs of internal secretion. It would thus be easily comprehensible that this effect might differ somewhat with differences of individual constitution.

"GANGRENE."

A similarity has long been recognized between the gangrene of human cases and the deficiency of wound-healing in totally depancreatized dogs. The dry gangrene which is the commonest clinical form arises always on a basis of arteriosclerosis, and as dogs seem to be not subject to arteriosclerosis, they do not exhibit this form of gangrene. The other form of so-called gangrene, consisting in superficial infections and ulcers which spread instead of healing, occurs in only a small minority of either dogs or patients, and about as frequently in one as in the other. Mention was made in Series I[4] of dog B2-56, which showed unusually rapid downward progress and cachexia. With this there was a development of trophic ulcers as marked as in any human case. One of these perforated into the right elbow-joint and gave rise to a large abscess in the axilla. Other examples are the following:

Dog B2-11.

Female; mongrel; black and white, aged two years; good condition; weight, 6 kilos. November 20, 1913, removal of pancreatic tissue weighing 16.9 gm. Remnant about main duct estimated at 0.6 gm. ($\frac{1}{29}$). Though the remnant was small and the feces accordingly somewhat bulky, the dog showed no more than the usual glycosuria and other symptoms on meat diet. Early in December something caused a trivial abrasion of the right ankle-joint. By December 8 the whole leg was hot and swollen, without any definite sinus leading from the point of abrasion. Incisions released considerable pus but did not stop the spread of the infection. Death occurred with pneumonia December 11, at a weight of 3 kilos.

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[4] Jour. Exp. Med., 1920, xxxi, 560 and 594.

Dog B2–46.

Male; mongrel; yellow, aged four years; thin but strong; weight, 23.25 kilos. March 26, 1914, removal of pancreatic tissue weighing 32.5 gm. Remnant about main duct estimated at 5.9 gm. ($\frac{1}{6}$ to $\frac{1}{7}$). Glycosuria remained absent until bread feeding was begun on March 30, and was heavy thereafter (up to 6 per cent. in above 2000 c.c. of urine). The asthenia was more marked than in any of the dogs mentioned above as examples of asthenia, and the susceptibility to "trophic" or progressive ulceration equalled or exceeded that of human cases. Death occurred by hemorrhage on April 13.

Other examples will be omitted for the sake of brevity. Certain facts are available concerning the cause of the abnormal liability to infection and necrosis: (1) It is not due to simple malnutrition, for carbuncles and intractable ulcers occur in obese diabetics who are apparently in nutritive equilibrium, and are much commoner among diabetics than among equally undernourished patients with other diseases; (2) it is known that control of the glycosuria and hyperglycemia is the most important means of preventing or curing these conditions, and for this reason speculation has attributed their cause to direct injury of the excess of sugar by osmotic or other action or to the favoring influence of sugar upon bacterial growth. A previous attempt[5] failed to produce any of the supposed consequences of sugar excess by long-continued injections of glucose or other sugars. In more recent experiments subcutaneous injections of 0.1 gm. phlorizin daily have been found to keep the blood sugar of totally depancreatized dogs at a low level, but their impaired healing power, resistance to infection and other disorders have not been in the least benefited. Furthermore the immense majority of partially depancreatized dogs exhibit healing and resisting power practically identical with the normal, even when their hyperglycemia and glycosuria exceed those of totally depancreatized dogs in both degree and duration. The mere loss of sugar and nitrogen from the body is evidently not responsible, for totally phlorizinized dogs bear operations reasonably well. The factor of dryness of the tissues is also thus controlled, for some phlorizinized or partially depancreatized dogs evidently undergo greater desiccation than the average totally depancreatized dog. (3) The actual endocrine deficiency, in addition to any of the above factors, must be invoked here as in the case of asthenia. The almost uniform difference between totally and partially depancreatized animals is thus explainable, and the special incidence in individual animals or patients may be accounted for by constitutional variations in resistance and the occurrence of predisposing injuries.

Allen, F. M.: Studies Concerning Glycosuria and Diabetes, 1913, chapter iii.

COLLAPSE AND PROSTRATION AS RELATED TO GLYCOSURIA.

Examples were previously given[6] of the prevention of glycosuria by weakness or prostration, and numerous others might be added from the present series. Dog D4–76 underwent operation on January 19, 1917, and died January 22 from necrosis of most of the pancreas remnant. Here the diabetes should have approached that of a totally depancreatized animal, but the principal symptom was prevented by intoxication. The instance is mentioned because of the similarity to some human cases of fulminating pancreatitis. In Series I, reference was made to animals in which glycosuria was stopped and the progress of diabetes halted by distemper or other causes of anorexia and emaciation. Such animals sometimes later enjoyed excellent health and a high food tolerance in consequence of their spontaneous undernutrition treatment. When the diabetes has become established in a sufficiently severe form, it cannot be halted by fasting or any other known means. In the writer's experience totally depancreatized dogs as well as the partially depancreatized ones with the severest diabetes ordinarily die after continuous fasting or any intercurrent illness or accident with heavy glycosuria present to the end. In the monograph (1913) already mentioned, references were made to theliterature concerning absence of glycosuria in totally depancreatized animals after such extreme procedures as removal of the liver or adrenals, or high section of the spinal cord. Any therapeutic significance of such results can be imagined only on the basis of two fallacies, one the confusion between glycosuria and diabetes and the other the indefensible doctrine of diabetes as a pure overproduction of sugar. If it be believed that an animal is diabetic because it cannot assimilate carbohydrate without the internal secretion of the pancreas, obviously the removal of some other organ cannot restore the lost power. Likewise the cessation of glycosuria in occasional totally depancreatized animals in the last hours of life has no therapeutic significance. The very fact of total absence of the pancreas renders such animals unfit for therapeutic experiments unless it is a question of some extract or other agent which can replace the pancreatic function. The results of the undernutrition treatment of patients and partially depancreatized animals are significant for both theory and practice because it can be shown that they do not represent a mere suppression of glycosuria by cachexia, but accomplish an actual raising or preservation of the power of food assimilation and permit a long or indefinite continuance of life.

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[6] (Ibid.), p. 492.

PROLONGED CACHEXIA.

The following are rare instances in which diabetes seemed to be superseded by some unknown cachectic condition, producing results different from those of simple undernutrition. Cats seem to be more liable than dogs to this abnormality.

Cat A1–91.

Male; gray striped; middle aged; slightly thin; weight 3.1 kilos. January 13, 1914, removal of pancreatic tissue weighing 5.8 gm. Remnant about main duct estimated at 1.8 gm. (about $\frac{1}{4}$). There was glycosuria on milk and meat diet and none on meat alone. The appetite and health seemed excellent. The glycosuria was allowed to continue and increase up to 5 per cent. in 455 c.c. urine on February 6. February 7, at a weight of 3.2 kilos, fasting was begun. The glycosuria immediately fell to traces, rose to a moderate reaction on February 10, then fell and was absent after February 12. February 16, at a weight of 2.6 kilos, feeding was begun with 20 gm. cooked beef-lung, increasing gradually until on February 23, 140 gm. lung and a live mouse were fed. The weight meanwhile had been falling rapidly to 1.8 kilos; the cat retained appetite and appeared well except for remarkable weakness and weariness. Lung, suet and raw pancreas were then fed as abundantly as possible. The digestion seemed rather poor, as indicated by bulky formed feces, but the cachexia was more advanced and progressive than is seen in plain fasting. Death occurred February 26, and no cause could be found at autopsy. The microscopic examination of liver, kidneys, adrenals and thyroid was negative. The pancreas remnant, normal in appearance and consistency, weighed 1.8 gm. It was fully normal microscopically; the acini were well filled with zymogen; islands were abundant and free from vacuolation.

Cat A1–94.

Female, adult; white and black; thin; weight, 2 kilos. January 21, 1914, removal of pancreatic tissue weighing 3.7 gm. Remnant about main duct estimated at 0.8 gm. ($\frac{1}{5}$ to $\frac{1}{6}$). The animal refused food except for a trifle of milk, and the highest glycosuria was 0.5 per cent. in 25 c.c. urine. Death occurred on January 25, with urine sugar-free, at a weight of 1.6 kilos. Autopsy showed no cause. The pancreas remnant weighed 0.6 gm., and was normal in acini and islands.

The history of cat A1–95 was closely similar.

Some atypical results of this character caused the writer formerly[7] to conclude wrongly that cats are unsuitable for diabetic experiments.

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[7] (Ibid.), p. 502.

Cat A1–96.

Male; gray and white; large, strong adult; excellent condition; weight, 3.4 kilos. February 9, 1914, removal of pancreatic tissue weighing 5.6 gm. Remnant about main duct estimated at 1.4 gm. ($\frac{1}{5}$). Glycosuria was produced at first only by milk. It was present March 1 to 23 on meat diet, then ceased spontaneously. With addition of milk it was present March 30 to April 9. On this date two tiny fragments of pancreas, with an aggregate weight of 0.15 gm., were removed for microscopic study. Then on fasting, glycosuria was absent after April 11. A diet of beef-lung or liver was begun with 50 gm. on April 13, increased rapidly to 300 gm. and then *ad libitum*. The cat meanwhile rapidly lost weight and strength without glycosuria, and died April 26, at a weight of 1.9 kilos. The autopsy revealed no gross or microscopic cause of the condition. The pancreas remnant weighed 2.25 gm. Microscopically the tissue removed April 9 was normal except for marked vacuolation of islands. At autopsy there was some interlobular fibrosis; the acini were nearly empty but otherwise normal; islands were scarce in some sections, abundant in others, with most of their cells normal but a few showing slight persisting vacuolation.

In several dogs glycosuria has been unexpectedly absent or has ceased for unknown cause after it has been present for a longer or shorter time. These instances of cachexia have confirmed the previous conclusions[8] that the duration of life is generally far shorter than in cases in which diabetes develops in typical form. The most marked example of prolonged cachexia was the following:

Dog D4–70.

Male; mongrel; white and black; shaggy; aged four years; medium nutrition; weight, 15.5 kilos. January 10, 1917, removal of pancreatic tissue weighing 31.6 gm. Remnant about main duct estimated at 2.6 gm. (about $\frac{1}{13}$). There was no glycosuria until bread and milk was fed on January 13, causing a slight reaction which disappeared on the same diet. Beginning January 18 a diet of bread and 200 gm. glucose maintained glycosuria until January 23, when it ceased. Thereafter the dog ate the same full pan of bread, with 300 gm. glucose, 200 gm. lung and 100 gm. suet without glycosuria. Beginning January 27, analyses of urine and feces were performed on a diet of 200 gm. lung, 250 gm. bread and 100 gm. suet, which showed only a moderate deficiency of food absorption; also a genuinely high tolerance was demonstrated by an intravenous glucose test and a series of blood sugar analyses, but all these records were lost. February 10, 0.5 gm. phlorizin suspended in oil was injected subcutaneously, and heavy glycosuria continued until February 15, indicating a full ability to form and excrete sugar under this stimulus. The weight had mostly remained low, between 13 and 14 kilos, but rose by April 4 to 16.4 kilos. At this weight the feeding of bread and soup *ad libitum* with 100 gm. glucose brought on glycosuria, which ceased promptly when the diet was changed to 400 gm. lung and 200 gm. suet. By May 4 the dog was still lively and happy, with enormous appetite, but was showing hair loss and unsteadiness of legs. Because the symptoms resembled those of fat intoxication (produced in normal dogs by diets too high in fat and low in protein) the diet was changed on May 22 to lung and bread, with milk occasionally, and bonemeal to supply salts. On June 12 and July 27 small portions of pancreas were removed for microscopic examination without giving rise to glycosuria. The pancreas remnant appeared normal grossly and microscopically. The body weight fell as low as 10.3 kilos, notwithstanding edema, but rose later to 12.5 kilos. Death occurred, apparently from simple weakness, on September 27. The pancreas remnant, slightly firm and nodular, was in free communication with its duct, and weighed 2.9 gm. Microscopically it showed slight fibrosis, interacinar as well as interlobular, but the acini were large and well filled and the islands abundant and normal. Gross and microscopic examination of the other viscera revealed no abnormalities to account for the condition.

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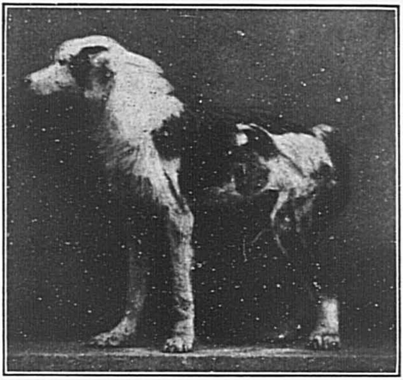
[8] (Ibid.), p. 500.



The above photograph was taken on July 5. The dog unfortunately was not photographed when normal, but was a rather handsome animal with long thick hair. The hair loss is seen on the head and ears, trunk, limbs, and the naked end of the tail visible between the legs. Edema without evidences of nephritis is occasionally seen in cachectic dogs, even without pancreas operations. It was greater here in the hind than in the front limbs, and was not like myxedema, but consisted in an accumulation of clear fluid which flowed freely from a needle puncture. The dog remained in excellent spirits throughout. Signs of sexual activity were completely lacking, and the animal was somewhat silly in mentality, as J. H. Pratt has stated[9] concerning young dogs with pancreatic atrophy.

Conclusions. 1. In addition to some acute deaths from unknown causes shortly after partial pancreatectomy, examples were given of diabetic asthenia and diabetic gangrene in animals, which add another detail to the resemblance between clinical and experimental diabetes. Reasons were given for considering both the asthenia and the gangrene as due not to simple malnutrition, hyperglycemia, glycosuria or other causes, but rather to the specific endocrine deficiency.

2. Examples were also given in which the diabetes of dogs and cats was replaced by a fatal cachexia of unknown nature. It is not certain that the condition in all these instances was the same. Malnutrition due to impaired digestion or intestinal absorption was probably one factor, but the results seem to differ in some respects from simple undernutrition, and may possibly bear some relation to the metabolic alterations in states of prostration which suppress glycosuria even after total pancreatectomy.

3. It is highly important to distinguish the mere suppression of glycosuria by some injury, poison or cachexia from genuine control or improvement of the diabetes. It is thus impossible to use totally depancreatized dogs for any therapeutic experiments, unless for testing some agency which is supposed to replace the internal pancreatic function. The results of the undernutrition treatment of animals and patients are distinguished from mere cachectic suppression of glycosuria by the fact that the power of food assimilation is demonstrably strengthened, the general health improved and life lengthened instead of shortened.

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[9] Personal communication. Also Jour. Am. Med. Assn., 1912, lix, 322–325.